Citation	Abdelmalak BB, Knittel J, (2012), **Preoperative blood glucose concentrations and postoperative outcomes after elective non-cardiac surgery: an observational study.** Nat Rev Endocrinol. 2012 Feb 7;8(6):374-8.
Archived version	Author manuscript: the content is identical to the content of the published paper, but without the final typesetting by the publisher
Published version	http://dx.doi.org/10.1093/bja/aet297
Journal homepage	http://bja.oxfordjournals.org/
Author contact	your email greet.vandenberghe@med.kuleuven.be your phone number + *32 (0)16 344021*
IR	https://lirias.kuleuven.be/handle/123456789/420978

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Preoperative Blood Glucose Concentrations and Postoperative Outcomes Following Elective Noncardiac Surgery: An Observational Study

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Short title: Preop blood glucose and noncardiac surgery outcomes

Preliminary results were presented at the American Society of Anesthesiologists Annual Meeting, 18 October 2010, in San Diego, CA.

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SUMMARY

Background: The association between preoperative blood glucose (BG) concentration and outcomes after noncardiac surgery and the impact of the diabetes diagnosis status remain unclear. We tested two hypotheses: that preoperative BG is related to surgical outcomes; and that this relationship depends on the diabetes diagnosis status of the patient.

Methods: We retrospectively analysed data on 61,536 consecutive elective noncardiac surgery patients treated at our tertiary care facility. logistic regression models were used to test the hypotheses before and after adjustment for baseline patient characteristics. Our primary outcome was a composite of in-hospital serious complications and mortality. A second primary outcome was one-year mortality.

Results: The crude incidence of the composite in-hospital outcome was significantly related to preoperative BG ($P<0.001$), but not after covariable adjustment ($P = 0.40$). This relationship did not significantly differ between patients with and without diagnosed diabetes ($P = 0.09$). One-year mortality was significantly related to preoperative BG, both univariably ($P<0.001$) and after covariable-adjustment ($P<0.001$). Patients with diagnosed diabetes and preoperative euglycaemia generally had worse one-year mortality than patients without diabetes and the same BG (e.g., OR [95% CI] of 1.27 [1.06, 1.53] at 6 mmol litre^{-1} [108 mg dl $^{-1}$], $P=0.003$). Conversely, hyperglycaemic patients with diagnosed diabetes displayed a significantly lower one-year mortality than hyperglycaemic patients without diabetes (OR [95% CI] of 0.58 [0.44, 0.77] at 12 mmol litre^{-1} [216 mg dl $^{-1}$], $P<0.001$).

Conclusions: For elective noncardiac surgery, preoperative hyperglycaemia should be given greater consideration in patients without diabetes than in patients with diagnosed diabetes.

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Keywords: Anaesthesia-general; Metabolism-hyperglycemia; Surgery-non-cardiac; Diabetes; Complications-death

Current data offer no guidance on whether an elective procedure should be cancelled in light of a given level of hyperglycaemia. Lack of guidance stems in part from the fact that the association between preoperative blood glucose concentration and postoperative complications after noncardiac surgery is not very clear. In noncardiac surgery patients, preoperative blood glucose levels above 11.1 mmol $litre^{-1}$ (200 mg dl^{-1}) have been shown to be associated with a 2.1-fold higher risk in overall 30-day mortality and a 4-fold higher risk of 30-day cardiovascular mortality.[1] Hyperglycaemia was associated with a 4-fold increased risk of pulmonary embolism (PE) in a small study of patients undergoing total joint replacement.[2] However, these studies were limited; for they evaluated only particular outcomes (PE and 30-day mortality) in specific noncardiac surgery subpopulations. Moreover, no data are available on the association between preoperative hyperglycaemia and serious postoperative complications as well as one-year mortality in a large cohort of patients undergoing different noncardiac surgical procedures.

In the intensive care unit (ICU) setting, the effect of blood glucose concentrations on outcomes appears to be dependent on diabetic status. Hyperglycaemia upon admission to the ICU has been shown to be an independent risk factor for in-hospital mortality only in patients without diabetes.[3] Hyperglycaemia during the ICU stay was associated with significantly increased ICU mortality in patients without, compared to those with diabetes mellitus suggesting that hyperglycaemia may bear different clinical and biological implications in patients depending on their chronic metabolic status.[4] Furthermore, a meta-analysis of two randomised trials showed reduced mortality with intensive insulin therapy in ICU patients was evident only in patients without a history of diabetes mellitus.[5] However, in elective noncardiac surgery, the impact of a patient's diabetes diagnosis status on the association between preoperative glucose concentrations and postoperative outcomes and mortality has not been investigated.

We tested the hypotheses that in elective noncardiac surgery patients, preoperative blood glucose concentration is related to postoperative in-hospital outcomes and to one-year mortality, and that this relationship is more pronounced in patients without a diagnosis of diabetes mellitus.

METHODS

Data were extracted with the Cleveland Clinic Institutional Review Board (IRB)'s approval of the Anaesthesiology Institute's Perioperative Health Documentation System (PHDS) for quality improvement purposes and for research on patients who present for noncardiac surgery. The need for informed consent was waived. Data were aggregated from the electronic anaesthesia information system and hospital electronic medical records (EMR). Supplemental demographic and clinical data in other institutional databases were imported into the registry either manually or through computer interfaces. Data validations were built into the registry to ensure the quality of data.

Selection and description of participants

The studied population was defined as patients undergoing elective noncardiac surgery at our institution between January 2005 and November 2009, and included only the most recent operation per patient. (Table 1) Patients were excluded if data were unavailable for the specified type of surgery or preoperative glucose concentration measurement. Patients with American Society of Anesthesiologists Physical Status (ASA PS) of > IV were also excluded.

Technical information

Glucose concentrations were measured by the central laboratory at the time of the pre-operative evaluation (as a part of a basic or complete metabolic panel) in patients who had significant past medical history including diabetes, and/or undergoing surgery of more than low risk. Moreover, in patients with a diabetes diagnosis, glucose concentrations were measured immediately pre-operatively by the point of care testing using Accu-Chek Inform system (Roche Diagnostics, Indianapolis, IN, USA). Each Accu-Check device was checked in three dimensions [linearity, inter-method (lab vs. meter), and meter-meter] and used only when acceptable results on all three metrics were found. Additionally, calibrations with low and high controls were performed daily to ensure continued high performance. Glucose measurement included in the analysis was the last value available before surgery documented in the EMR for a given patient. No glucose concentration measurements performed after the induction of anaesthesia for surgery was included . History of diabetes mellitus was screened for as follows: a Health Quest system which is an online system of patients' self-reporting is required to be completed by all surgical candidates and validated by a surgical team member. Also a history and physical examination is mandated to be completed within 30 days of surgery. Patients were considered diagnosed with diabetes if they had a history of either type 1 or type 2 diabetes, and/or receiving insulin or oral hypoglycemic medications.

During the time of the study, the target ranges for blood glucose control in the hospital were as follows: In the recovery room, <11.1 mmol $litre^{-1}$ (200mg dl^{-1})whereas in the ICU, it was 3.9-7.2 mmol $litre^{-1}$ (70-130 mg dl^{-1}) for the first two years, and 4.4-6.7 mmol $litre^{-1}$ (80-120 mg dl^{-1}) for the last three years; whereas on the regular nursing wards, it was 3.9-8.3 mmol $litre^{-1}$ (70-150 mg dl^{-1}).

In-hospital morbidity outcomes were identified by ICD-9 codes for postoperative complications. In addition, using laboratory measurements, we identified patients with postoperative myocardial infarctions (for details, see Table 2, second column). One-year mortality was determined through searching hospital EMR and the Social Security Death Index (SSDI) through mid-2011.

Statistical Analysis

First, a preliminary analysis was undertaken to study the relationship between preoperative blood glucose concentrations and hemoglobin A1c (HbA1c) values, among those who had HbA1c measured within 90 days prior to the date of surgery. For this preliminary analysis, we used quantile regression.[6 7] Restricted cubic splines were used to model potential non-linear relationships.

To evaluate if preoperative blood glucose concentration was related to the incidence of each endpoint, we used logistic regression models. Using a model without covariates, we first estimated for a given outcome its crude (unadjusted) incidence as a function of preoperative glucose concentration. Natural cubic splines with five degrees of freedom were used to model potential nonlinearities in the incidence function (and for any continuous predictors used in the logistic regression models described henceforth). After estimation of the crude incidence function, we developed a multivariable model which estimated the incidence function after adjusting for potential confounding variables. These potential confounding variables are listed in Table 1.

Prior to multivariable modelling, a single approximate Bayesian bootstrap[7] imputation was used to impute missing potential confounder values (because only three patients had a history of cerebrovascular or transient ischaemic attack, we combined this variable with history of carotid disease for modelling purposes). The null hypothesis of no relationship between preoperative glucose and the outcome was evaluated within both the unadjusted and potential confounder-adjusted models using Wald chi-squared tests.

Since certain surgeries were represented by too few patients to accommodate direct adjustment (i.e., small cell sizes), we adjusted for type of surgery as follows: First, we aggregated patients' primary procedure into one of 244 categories of the U.S. Agency for Healthcare Research and Quality Clinical Classifications Software (AHRQ-CCS).[8] Next, three senior anaesthesiologists (BA, JF, MA) independently rated each of these 244 categories from 0 to 10 on a scale of surgical risk. The mean of the three raters' estimates of surgical risk was then used for adjustment in our multivariable models.

For the second hypothesis, regarding the differences between patients with and without a history of diabetes mellitus, we also used unadjusted and covariable-adjusted logistic regression models. We used the same covariables for adjustment as in the first analysis addressing the associations in the total patient population. In these models, relationships between preoperative glucose and the incidence of an outcome were estimated separately for patients with and without diagnosed diabetes. Odds ratio functions of baseline glucose concentration, comparing patients with and without diagnosed diabetes, were also estimated. Using respective Wald chi-squared tests, we evaluated the null hypothesis of similar relationships between the two populations before and after covariable adjustment. Provided there was evidence of significantly different relationships between patients with diabetes diagnosis and those without diabetes, we used a generalized Wald test,[9, 10] to evaluate whether or not glucose was related to the outcome within each respective patient population.

R statistical software version 2.15.1 (The R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analysis. The Type I error rate for our study was fixed at 0.05 by controlling the outcome-specific Type I error rate at 0.025; the Bonferroni correction for multiple comparisons within an outcome was also implemented, where applicable.

RESULTS

Data from 75,654 ASA PS I-IV patients undergoing elective noncardiac surgery at our institution between January 2005 and November 2009 were available. Excluded were patients with missing preoperative blood glucose concentration (N = 12,060) as well as patients with missing data on type of surgery (N = 1,306) and patients with missing preoperative medications data (N = 752). (see flow chart, Figure 1) The resulting sample comprised 61,536 patients. Patient and pre-surgical characteristics are summarised in Table 1. The overall median [1st quartile, 3rd quartile] serum glucose concentration for the sample was 5.2 [4.7, 6.1] mmol litre^{-1} (94 [84, 110] mg dl^{-1}); median glucose for patient with diagnosed of diabetes was 7.0 [5.5, 9.5] mmol litre^{-1} (126 [100, 171] mg dL^{-1}) and 5.1 [4.6, 5.7] mmol litre^{-1} (92 [83, 103] mg dl^{-1}) for patients without diabetes diagnosis. Of the 51,809 patients without diagnosed diabetes, 1,616 (3.1%) had a blood glucose value greater than 8 mmol litre^{-1} (144 mg dl^{-1}) and 390 (0.8%) had a blood glucose greater than 11 mmol litre^{-1}(198 mg dl^{-1}).

There were 3,929 patients who had available HbA1c values measured within 90 days prior to their operation. Quantile regression curves estimating from these cases the 10th percentile, first quartile, median, third quartile, and 90th percentile of serum glucose as a function of hemoglobin A1c are shown in Appendix 1.

Individual outcomes comprising the composite in-hospital outcome were uniformly represented (incidences of 1-3%) except for mortality (0.5%) and wound disruption (0.5%) (Table 2). Overall, the crude incidence (Bonferroni-adjusted 95% CI) was 9.91% (9.65%, 10.19%). The crude incidence was significantly related to preoperative blood glucose concentration (P<0.001, Figure 2a), ranging from approximately 8-11% for patients with glucose concentration of 4-6 mmol litre^{-1}(72-108 mg dl^{-1}), to approximately 12-16% for those with glucose concentration above 7 mmol $litre^{-1}$(126 mg dl^{-1}). However, the incidence was not significantly related to preoperative blood glucose concentration after adjustment for covariables (P=0.40, Figure 2b).

The crude incidence (Bonferroni-adjusted 95% CI) of one-year mortality was 5.41% (5.24%, 5.60%). This crude incidence was significantly related to preoperative blood glucose concentration, reaching a minimum of 3.5% at a concentration of 4.7 mmol $litre^{-1}$ (85 mg dl^{-1}) and increasing to >9% for preoperative blood glucose levels above 10 mmol $litre^{-1}$ (180 mg dl^{-1}) (Figure 2c). After covariable adjustment, a statistically significant relationship remained (P<0.001, Figure 2d).

There were 9,727 patients (15.8%) who were previously diagnosed as having diabetes mellitus. The crude incidence of the composite in-hospital outcome for patients with diabetes was approximately 15% regardless of preoperative blood glucose level, whereas for patients without diabetes, the incidence ranged from 7-9% for patients with glucose concentration of 3.3-5.5 mmol $litre^{-1}$ (60-100 mg dl^{-1}) to 13-15% for patients whose preoperative blood glucose concentration was above 8 mmol $litre^{-1}$ (144 mg dl^{-1}) (Figure 3a). However, after adjustment for covariables, we found that the relationship between preoperative blood glucose and the probability of postoperative complication did not significantly differ between patients with and without diabetes mellitus (P=0.09; Figure 3b).

The crude incidence of one-year mortality was estimated to be approximately 8-11% across the range of preoperative blood glucose concentrations for patients with diabetes, except for those with concentrations 3.3-5.0 mmol $litre^{-1}$(60-90 mg dl^{-1}), where the incidence was approximately 10-14% (Figure 3c). The crude incidence for patients without diabetes was strongly related to preoperative blood glucose, ranging from 3% to 5% for patients with glucose concentrations of 3.3-5.5 mmol litre^{-1} (60-100 mg dl^{-1}) to >12% for patients with preoperative blood glucose above 12 mmol litre^{-1}(216mg dl^{-1}). After adjusting for covariables, significantly different relationships between patients with and without diabetes mellitus remained ($P<0.001$; Figure 3d). The generalized Wald test p-values were $P = 0.33$ for the patients with diagnosed diabetes and $P<0.001$ for the patients without, indicating no significant relationship between glucose concentration and one-year mortality for patients with diagnosed diabetes but a strong relationship among patients without that diagnosis.

Adjusted odds ratio curves comparing patients with and without diabetes mellitus on both primary endpoints are shown in Figure 4 and summarised numerically in Appendix 2. The adjusted odds ratio for the composite outcome was generally not significantly different from 1.0 over the range of preoperative blood glucose concentrations. On the other hand, the adjusted odds ratio for one-year mortality was significantly and nonlinearly related to preoperative blood glucose. Based on the point wise confidence bounds in Figure 4, patients with diagnosed diabetes and with preoperative blood glucose of 3.6-4.9 mmol litre^{-1} (65-88 mg dl^{-1}) had significantly increased odds of mortality compared with patients without diabetes diagnosis. This odds ratio declined as preoperative blood glucose increased. Patients with diabetes and preoperative blood glucose >8.5 mmol litre^{-1} (153 mg dl^{-1}) had significantly lower odds of mortality than patients without diabetes.

DISCUSSION

We evaluated the statistical relationship between preoperative blood glucose concentration and postoperative in-hospital outcomes as well as one-year mortality, and the impact of a diagnosis of diabetes mellitus on these relationships, in a very large cohort of patients undergoing elective noncardiac surgery. In our cohort, preoperative hyperglycaemia was directly related to poor postoperative in-hospital outcomes, as well as one-year mortality in the univariable model for all patients. In the multivariable model, the independent association between hyperglycaemia and one-year mortality, but not in-hospital composite outcome, remained significant. A preoperative diagnosis of diabetes mellitus significantly altered these associations. For a given level of hyperglycaemia, patients with diabetes mellitus had a lower risk of 1-year mortality, whereas for low to normal preoperative blood glucose concentrations, patients with diabetes mellitus diagnosis had a higher risk of death compared to patients without diabetes.

In other words, the relationship between glucose and 1-year mortality was weak (a flat curve) if patients were already diagnosed with diabetes. Conversely, if patients did not have diabetes diagnosis, there was a clear increasing rate of 1-year mortality once glucose concentration increased. That is not to say that diabetic status is not important. If one compared patients without diabetes and normal glucose concentrations (i.e. true negatives) against those with diagnosed diabetes with normal glucose concentrations – so a situation where missed diabetes diagnosis would not be an issue – mortality is higher among patients with diagnosed diabetes ."

Our results on in-hospital outcomes appear at variance with results from prior studies performed on noncardiac surgery patients. Preoperative hyperglycaemia (>11.1 mmol litre^{-1}[200 mg dl^{-1}]) was associated with a 4-fold increased risk of pulmonary embolism in a small study of patients undergoing total major joint replacement.[2] In noncardiac, nonvascular surgery patients, preoperative blood glucose levels greater than 11.1 mmol L^{-1} (200 mg dl^{-1}) have been associated with a 2.1-fold increased risk in overall 30-day mortality.[1]

An intriguing finding of our current study is that preoperative blood glucose was independently related to long-term outcomes (one-year mortality) and not to poor short-term in-hospital outcomes. A possible explanation for this finding is that preoperative hyperglycaemia reflects a chronic risk for death independent of the surgery. Another explanation may lie in the pro-inflammatory effect of hyperglycaemia, which could affect one-year mortality, especially given that HbA1c % generally increased with increasing blood glucose concentrations—indicating a chronic process. Blood glucose concentration has been shown to be independently related to C-reactive protein (CRP) levels (a marker of inflammation) in healthy subjects. CRP levels increased continuously across the spectrum of fasting blood glucose concentrations, even within the normal range.[11] However, the impact of such a pro-inflammatory response may not be clinically evident immediately. Milazzo and colleagues identified preoperative elevated concentrations of CRP as a predictor of recurrent ischaemia up to six years postoperatively.[12]

In our study, patients with diagnosed diabetes mellitus and preoperative blood glucose >8.5 mmol $litre^{-1}$ (153 mg dl^{-1}) had significantly lower odds of mortality than patients without diabetes diagnosis who had similar preoperative blood glucose concentrations. On the other hand, patients with diagnosed diabetes mellitus and preoperative blood glucose within 3.6-4.9 mmol $litre^{-1}$ (65-88 mg dl^{-1}) had a higher one-year mortality compared not only to patients without diabetes diagnosis with similar levels, but also to patients with diagnosed diabetes and higher preoperative blood glucose levels.

Patients without diabetes diagnosis who are hyperglycaemic, probably have diabetes albeit undiagnosed and thus untreated. Early diagnosis and treatment of diabetes may lessen its burden and delay its associated complications.[13-14] In an earlier study we showed that 21% of noncardiac surgery patients without a diagnosis of diabetes are hyperglycaemic and more than half of those have undiagnosed diabetes.[15] Similar findings have been also reported by Hatzakorzian and colleagues.[16] While previously fasting glucose concentrations were used to diagnose diabetes,[17] more recently, HbA1c has been advocated to be used as a screening test to diagnose diabetes[18-19]

A confounding factor, however, is that clinicians may have been more inclined to monitor and eventually to treat abnormal perioperative blood glucose levels in patients with a diagnosis of diabetes, but not those without that diagnosis. This differential management is in part explained by clinicians' belief that sensitivity to IV insulin varies depending on prior treatment with insulin.[20] In addition, anaesthesiologists are concerned about hypoglycaemia because symptoms are masked by general anaesthesia and sedation.[21] Hence, clinicians are more reluctant to treat hyperglycaemia in patients without diabetes diagnosis; because aggressive insulin protocols in cardiac surgery and in critical care patients have been shown to evoke considerably high rates of hypoglycaemia.[22-25]. Such a different treatment strategy in patients with and without diabetes diagnosis may have introduced a bias in our observations. Furthermore, patients with preoperative hyperglycaemia who are not diagnosed with diabetes likely had no access to quality general medical care (or poor compliance with maintaining following up with accessible general medical care). One can certainly make the argument that the higher the degree of preoperative glucose concentration, the worse the degree of poor medical care. Needless to say, poor medical care would be expected to be major determinant of subsequent outcomes.

And finally, in patients with established type 2 diabetes, glycaemic thresholds for counter-regulatory hormone secretion can be altered. Symptoms of hypoglycaemia and the onset of counter-regulatory hormone release can occur at normal glucose values.[26-27]

Findings similar to ours were reported by Whitcomb and colleagues,[3] who studied the impact of hyperglycaemia diagnosed upon ICU admission on outcomes. They concluded that hyperglycaemia upon ICU admission was an independent risk factor for in-hospital mortality only in patients without diabetes mellitus.

Although our analysis considered only preoperative glucose concentrations without adjusting for the effects of in-hospital glucose management for these patients, somewhat similar trends were observed in patients who had undergone glucose control strategies in the ICU. Van den Berghe and colleagues, reporting on the cumulative results of two large ICU randomised trials of intensive insulin therapy, concluded that such an intervention reduced mortality in all patients except those with an established diagnosis of diabetes mellitus.[5] Similarly, when Krinsley and colleagues evaluated 5,365 consecutive ICU patients, they found that mean glucose concentrations within the hyperglycaemic range were associated with higher mortality in patients without diabetes.[28] However, in their cohort, strict euglycaemia in patients diagnosed with diabetes was associated with a survival benefit in a multivariable model.

Likewise, Egi and colleagues observed increased mortality with increasing mean blood glucose concentrations in ICU patients without diabetes mellitus compared to patients with diabetes mellitus.[4] Graham and colleagues [29] showed that in the ICU, survivors with diagnosed diabetes had higher maximum glucose concentrations than did non-survivors without a diagnosed diabetes. Also, in their cohort the unadjusted mortality rates were significantly higher for patients with diabetes than for those without diabetes for a maximum glucose below 7.2

mmol litre^{-1}(129 mg dl^{-1}), but the opposite was the case for a maximal blood glucose level of 9.0 mmol litre^{-1}(162 mg dl^{-1}).

Cumulatively the data may suggest that expected benefits, if any, of tight glucose control may be determined by the pre-morbid diabetes diagnosis status.[24 30-31] More research is needed to improve our understanding of the complex association between blood glucose and outcome in noncardiac surgery patients, and randomised controlled studies are required [32-33]. For such studies, our data may help to define optimal blood glucose target levels for patients with and without diabetes. It should be highlighted as mentioned above that some investigations of tight glucose control in the ICU reported a higher risk of hypoglycemia.[24 31 34-35] Current recommendations thus favour more moderate targets in the range of 7.8-10.0 mmol litre^{-1}(140-180 mg dl $^{-1}$).[34 36]

Our study had some limitations. First, this was a retrospective review of a hospital database. As such, there remains the potential of unavailable data confounding the relationships of interest. Specifically, data on intra-operative and postoperative glucose management were unavailable. Accurate study of the relationships of interest while taking into account intra-operative and postoperative glucose management was impossible because this information was available for only a limited number of patients and such information is difficult to obtain in retrospect. Such analysis would require a large prospective clinical study. Second, we excluded patients for whom a preoperative blood glucose determination was unavailable, which may have introduced selection bias. Third, the generalisability of our results is limited by the fact that our cohort is from a single institution, and appears to be composed of patients at higher risk than average. (Indeed, approximately half of our patients were ASA PS ≥3). Moreover, our hospital had certain targets for in hospital glycemic management that may have influenced the results.

Finally, determination of in-hospital outcomes for our study relied on a search of discharge diagnosis ICD-9-CM codes. Although these codes are susceptible to under-reporting, we nevertheless believe that the discharge diagnosis codes are highly sensitive in determining which patients experience major in-hospital events. Moreover, there is no reason to believe that possible under-reporting could be associated with diabetes diagnosis status or with ascertainable preoperative glucose levels, to the extent that it would introduce bias in our estimates. Finally, the second primary outcome, one-year mortality, is a robust endpoint which is not affected by possible bias in the use of the ICD-9-CM codes.

In summary, in elective noncardiac surgery for a relatively high risk patient population, one-year mortality – but not the studied composite in-hospital morbidity endpoint – was independently associated with differences in preoperative blood glucose concentration. Patients without diabetes diagnosis and with preoperative hyperglycaemia showed higher one-year mortality than patients with diabetes with the same level of preoperative hyperglycaemia. Patients with diagnosed diabetes and preoperative glucose concentrations in the lower euglycaemic range had a higher one-year mortality than patients without diabetes with the same levels of preoperative euglycaemia.

Thus, clinicians should consider checking preoperative glucose concentration and screen for hyperglycaemia in patients without the diagnosis of diabetes as it is the case in those with diabetes diagnosis. On making the decision whether to proceed with or delay elective noncardiac surgery, hyperglycaemia should be considered more so in patients without a diabetes diagnosis compared to those with diabetes. Further research is required to confirm above findings and determine whether a specific perioperative glucose management strategy can improve outcomes following noncardiac surgery in patients with and without diabetes mellitus.

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Funding:

The study was supported entirely through internal departmental funds.

Declaration of Interests:

Nothing to declare

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Table 1: Summary of demographic, morphometric, and preoperative patient characteristics. Results presented as mean ± standard deviation, median [first and third quartiles], or percentages as appropriate

% Missing	Factor		All Patients *(N=61,536)*	Patients without diabetes diagnosis *(N = 51,809)*	Patients with Diabetes diagnosis *(N = 9,727)*
	Blood Glucose (mg/dl)		94 [84, 110]	92 [83, 103]	126 [100, 171]
	Age (years)		57.3 ± 15.5	56.3 ± 15.8	63.0 ± 12.9
	Male Gender		47.3%	46.5	51.7
1.6	Race	*Caucasian*	84.4%	85.6	77.9
		African American	11.9%	10.7	18.0
		Other	3.7%	3.7	4.1
	Year of Surgery		2007.1 ± 1.3	2007.1 ± 1.3	2007.1 ± 1.3
7.9	Body Mass Index (kg/m^2)		28 [24, 33]	27 [24, 32]	31 [27, 37]
0.2	ASA Physical Status	*I*	4.2%	5.0	0.1
		II	43.5%	48.3	18.0
		III	46.8%	42.5	69.9
		IV	5.4%	4.2	11.9
	Cancer		29.3%	29.1	30.3
	Hypertension		49.0%	43.3	79.6
	Coronary Artery Disease		13.2%	10.6	27.2
	History of CABG		4.9%	3.8	10.8
	History of PCI		5.2%	4.3	10.0
	Myocardial Infarction		5.5%	4.4	11.0
	Congestive Heart Failure		4.3%	3.1	10.7
	Ventricular Arrhythmia		1.3%	1.1	2.1
	Cerebrovascular Attack/TIA		0.0%	0.0	0.0
	Carotid Disease		0.1%	0.1	0.2
	Liver Disease		2.4%	1.7	5.9
	COPD		10.1%	9.5	13.3
56.7	Smoker		28.3%	29.6	21.1
	Deep Vein Thrombosis		1.4%	1.2	2.2
1.5	Serum Hematocrit (%)		40.8 ± 4.8	41.1 ± 4.6	39.3 ± 5.3
	Serum Creatinine >176.8 micromol litre $^{-1}$(> 2mg dl^{-1})		3.7%	2.9	7.9
	Surgical Risk Score#		4.1 ± 1.6	4.1 ± 1.7	4.2 ± 1.6

ASA= American Society of Anesthesiologists, CABG = Coronary artery bypass graft, COPD = Chronic obstructive pulmonary disease, PCI = Percutaneous Coronary Intervention, TIA = Transischemic attack

Table 2: Summary of complications comprising the in-hospital composite outcome.

Complication	Description	N (%)
In-Hospital Mortality		298 (0.48)
Neurological Complications	Nervous system complications, anoxic brain damage, cerebral hypoxia, stroke	387 (0.63)
Cardiac Complications	Cardiac arrest, cardiac insufficiency, cardiorespiratory failure, heart failure, myocardial infarction (postoperative CKMB ≥ 4.0% and CK ≥ 220 U/L or postoperative cardiac TnT ≥ 0.1 ng/ml)	1,492 (2.42)
Pulmonary & Respiratory Complications	Pneumothorax, pulmonary embolism/infarction, adult respiratory distress syndrome, pulmonary edema, acute respiratory insufficiency, shock lung, tracheostomy complications, transfusion-related acute lung injury	1,737 (2.82)
Infectious Complications	Ventilator-associated pneumonia, Mendelson's syndrome, pneumonia/aspiration, sepsis, septicemia, other postoperative infections	1,362 (2.21)
Urinary Complications	Urinary tract stoma, internal anastomosis and bypass of urinary tract, oliguria/anuria, acute renal failure/insufficiency, acute tubular necrosis.	748 (1.22)
Hemorrhagic Complications	Hemorrhage, hematoma, seroma	1,626 (2.64)
Wound Disruption	Dehiscence of operation wound, disruption of suture materials or other closure method, rupture of operation wound	325 (0.53)
COMPOSITE OUTCOME	*One or more of the above complications*	*6,100 (9.91)*

CKMB = creatine kinase myocardial band; TnT = cardiac troponin T

Figure legends

Figure 1: Study flow chart. ASA = American Society of Anesthesiologists

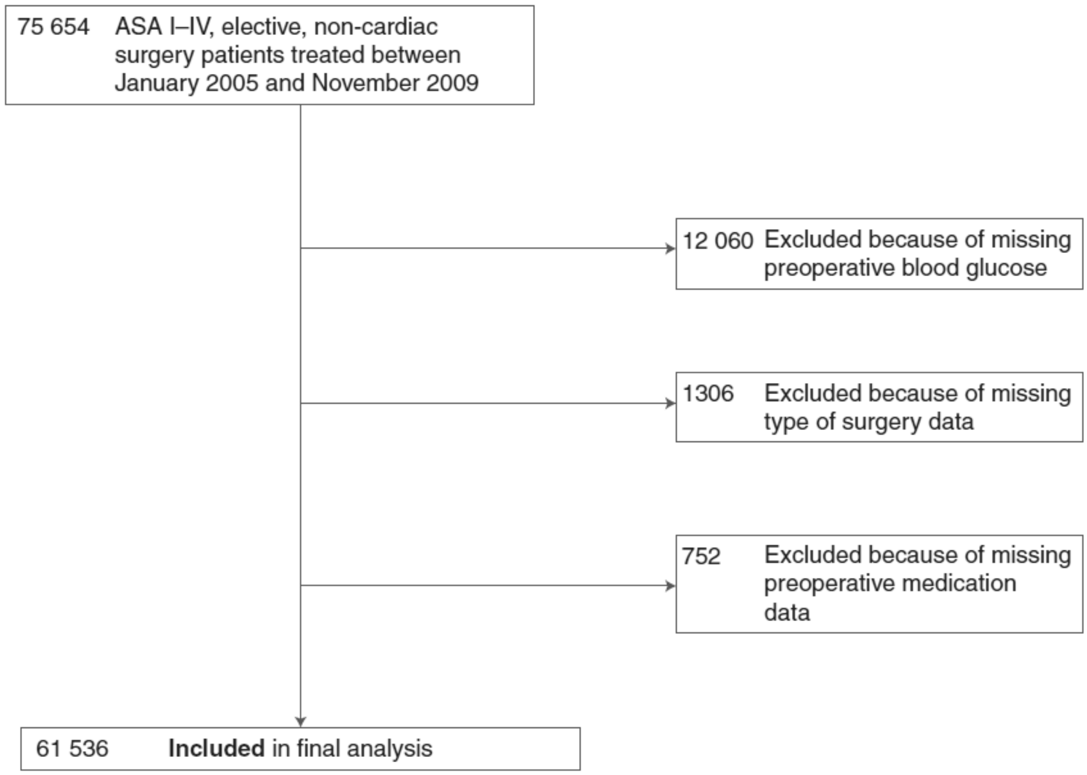

Figure 2: Crude and covariable-adjusted incidence of composite in-hospital morbidity/mortality and one-year all-cause mortality.

Estimates given as pointwise 95% confidence bands (confidence bands adjusted for simultaneous comparisons using the Bonferroni method). P-values from Wald tests assessing the relationship between baseline glucose and each outcome (statistical significance after the Bonferroni correction for simultaneous inference on two outcomes given by asterisks). Covariable-adjusted estimates are adjusted for all factors shown in Table 1. To convert to mg dl^{-1}, multiply the mmol $litre^{-1}$ value by 18.

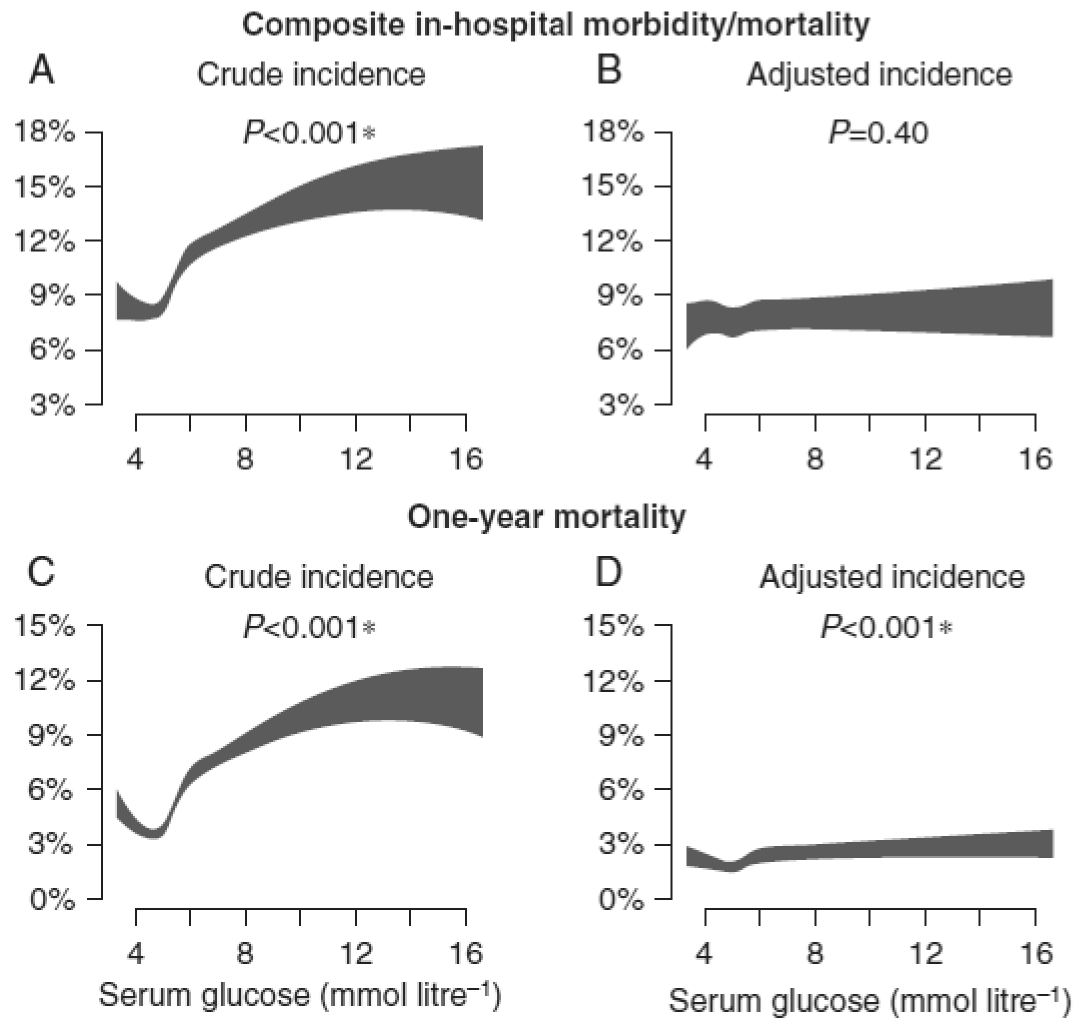

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Figure 3: Crude and covariable-adjusted incidence of composite in-hospital morbidity/mortality and one-year all-cause mortality, by baseline diabetic status.

Estimates given as pointwise 95% confidence bands (confidence bands adjusted for simultaneous comparisons using the Bonferroni method). P-values from Wald tests of equal relationships between baseline glucose and the respective outcome among the patients with and without a diagnosed diabetes (statistical significance after the Bonferroni correction for simultaneous inference on two outcomes given by asterisks). Covariable-adjusted estimates are adjusted for all factors shown in Table 1. To convert to mg dl^{-1}, multiply the mmol $litre^{-1}$ value by 18.

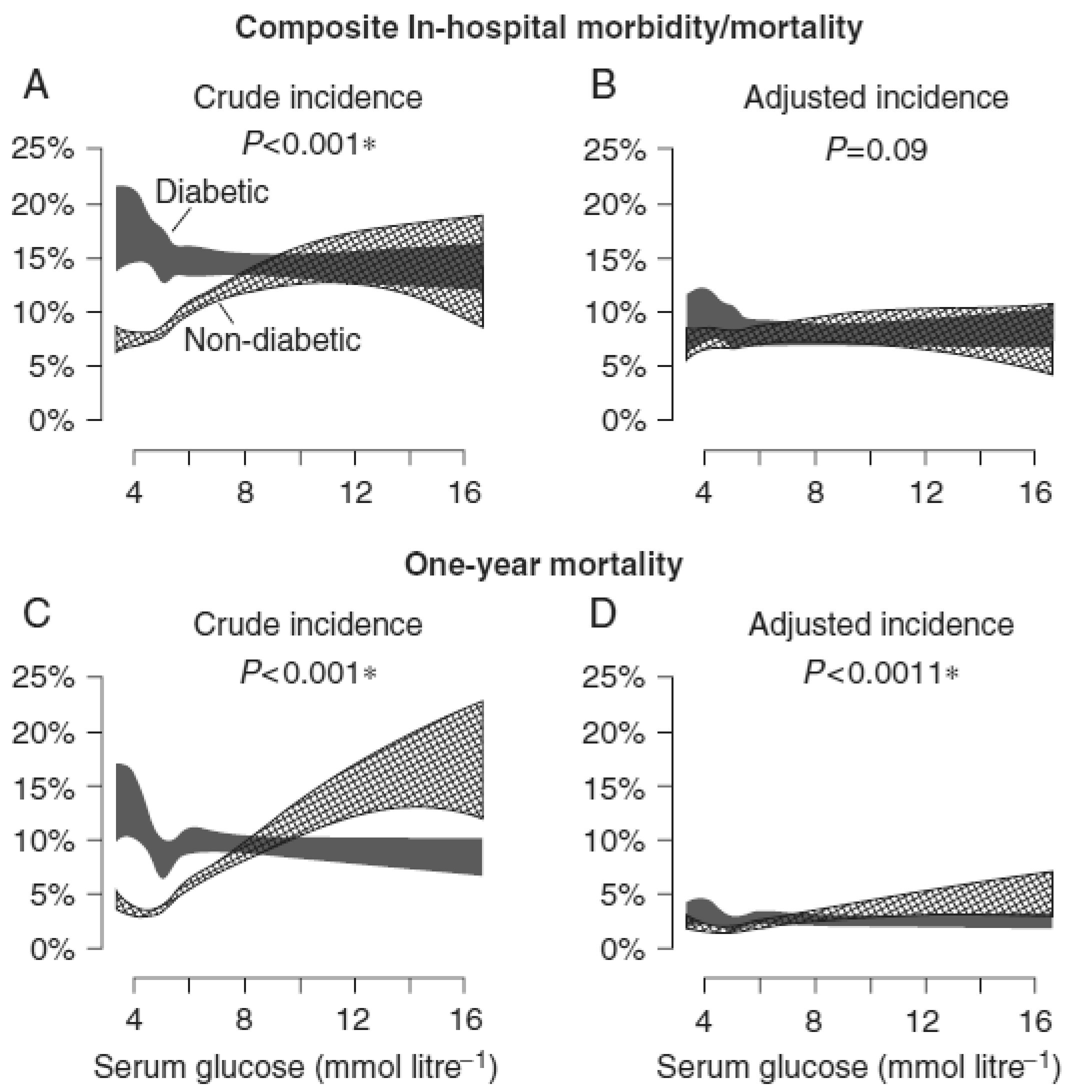
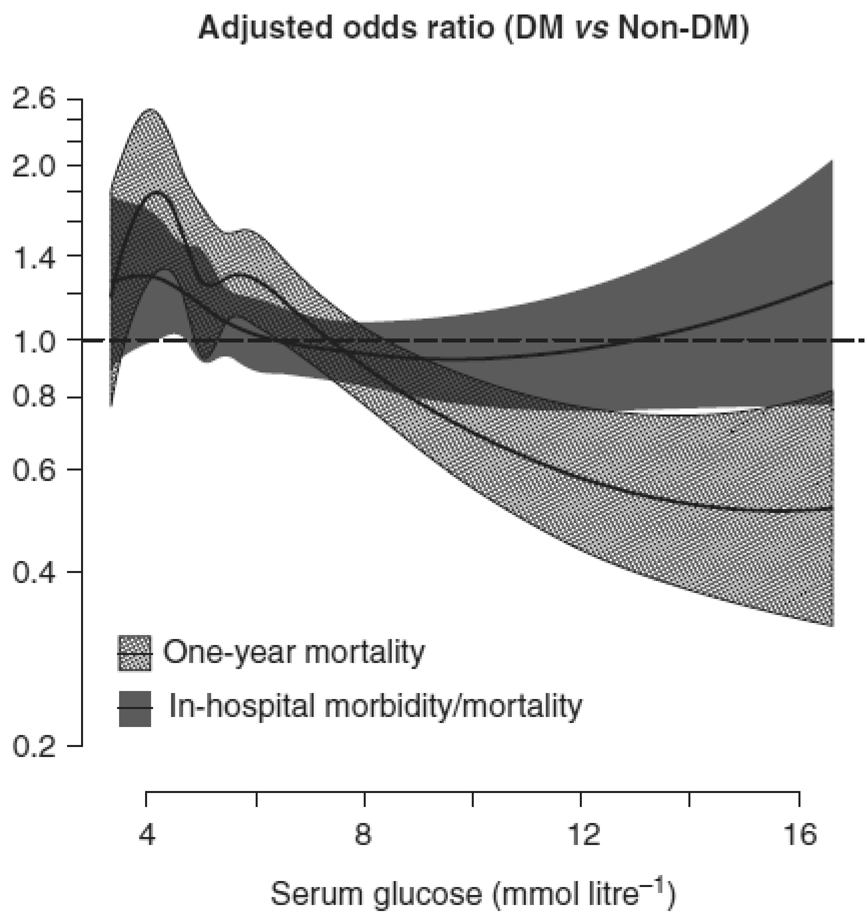


Figure 4: Covariable-adjusted odds ratio for composite in-hospital morbidity/mortality and one-year mortality as a function of preoperative serum glucose concentration.

Shaded regions represent pointwise 95% confidence intervals, adjusted for simultaneous inference on two outcomes. Odds ratios represent patients with diabetes diagnosis (DM) vs. those without diabetes diagnosis (Non-DM) . Estimates are adjusted for all factors shown in Table 1. To convert to mg dl^{-1}, multiply the mmol $litre^{-1}$ value by 18.



Appendices:

Appendix 1: Serum glucose as a function of haemoglobin A1c.

Displayed are estimates of the 10th percentile, first quartile, median, third quartile, and 90th percentile of serum glucose as a function of haemoglobin A1c. These curves thus summarize the distribution of serum glucose at each abscissa of haemoglobin A1c. Estimates obtained from respective quantile regression models and are estimated using restricted cubic splines with 5 degrees of freedom to allow for potential nonlinearities in the relationship.

To convert to mg dl^{-1}, multiply the mmol litre^{-1} value by 18

Appendix 2: Odds ratio estimates comparing patient with and without diabetes diagnosisfor composite in-hospital morbidity/mortality and for one-year mortality, as well as Wald test p-values testing the null hypothesis of odds ratio equal to 1. Odds ratios correspond to those given in Figure 4. P-values corresponding to statistically significant odds ratios after the Bonferroni correction are in italics.